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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,078	03/15/2004	Krzysztof Palczewski	0069509-000003	9475

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/801,078	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-22 and 35-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-22 and 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/2004, 6/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Applicant's election without traverse of Group III in the reply filed on February 8, 2008 is acknowledged.

2. Applicant has elected Group III in response to restriction requirement and elected the 11-cis-7-ring retinal species for the examination.

3. Claims 16 and 20 have been amended.

4. Claims 35-46 have been added.

5. Claims 1-15 and 23-34 have been cancelled.

6. Claims 16-22 and 35-46 are present for examination at this time.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 16-22 and 35-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are directed to "an opsin-binding synthetic retinoid" capable of binding to a mutant opsin protein with a reduced affinity for 11-cis-retinal to stabilize the opsin

protein and the loss of photoreceptor function is ameliorated. The description is inadequate to one of skill in the art to distinguish what the inventors were in possession of at the time of filing.

First, the claims and description define the compound by what it *does* and not what it *is*. Second, it does not adequately describe the degree of activity, effectiveness, or what is the desired amount of binding or stabilization or degree of amelioration would be needed for the compound to qualify. Additionally there is inadequate written description for which compounds would affect a mutant opsin protein having a reduced affinity for 11-cis-retinal. There are representative examples disclosed for 11-cis-7 ring retinal (e.g. cycloheptatrienylidene 11-cis-locked retinal), 9-cis-retinal (locked and unlocked forms), and 11-cis-retinal to affect the opsin/rhodopsin biosynthesis. However this is not sufficient to support the entire grouping claimed as generic forms such as those presented in the formulas (see I-XIII) as there are an insufficient amount of representative examples to anticipate the multitude of compounds claimed.

If fact, the specification addresses a screening method for ascertaining the possible compounds showing that the artisan was not in possession of the claimed compounds (see Page 5, paragraph 19, Page 12, paragraph 41).

The claims describe the compounds through a measurement of affecting protein stabilization or activity. This does not adequately describe which compound is addressed as it is inadequate to describe a product to be administered through the function of another mechanism, such as protein stabilization which can be affected by many conditions like temperature (e.g. fever) or trauma not related to the invention. As a

result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

For clarification, it is noted that in the nomenclature for 11-cis-7 ring retinal is not to carbon 7 but the “7” is recited to the size of the ring which results in a locked form of 11-cis retinal.

As only 11-cis-7 ring retinal, 9-cis-retinal, and 11-cis-retinal are specifically or known in the art to be applicable, only those compounds are to be considered.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 16-22 and 35-46 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "ameliorating" in claims 16-22 and 35-46 is a relative term which renders the claim indefinite. The term " ameliorating " is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term does not have any context or measurable standard to know what degree of change is sought for one of skill in the art to ascertain the metes and bounds of the invention.

11. Claims 16-22 and 35-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to a method of ameliorating loss of photoreceptor function in a vertebrate eye. The claims are indefinite as it is unclear what conditions by which loss of photoreceptor function are envisioned. The claims are unclear as they do not address what specific situations, conditions, or types (e.g. permanent, temporary, transient) of photoreceptor function loss the invention is directed to. In the current form, the claims could be directed to any manner of trauma to the eye, an injury to the eye, macular degeneration, conjunctivitis, natural eye strain, or a developmental disorder for example. It does not allow one of skill in the art to ascertain the metes and bounds of the invention.

12. Claims 16-22 and 35-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are unclear with respect to the pharmaceutical acceptable vehicle. As written, it is unclear if the opsin protein is part of the pharmaceutical vehicle. For the purposes of examination, the opsin protein is viewed to in the vertebrate eye and not in the vehicle.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 16-19, 22, 44, 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Hooser et al. (Rapid restoration of visual pigment and function with oral retinoid in a mouse model of childhood blindness).

Van Hooser et al. teaches the use of 9-cis-retinal through oral administration to a mice and human for the treatment of lack of 11-cis-retinal which directly affects rhodopsin, leading to reduction in the distinction of light sensitivity (meaning seeing the distinction between light and dark such as night vision and contrast sensitivity) and eventually blindness. The studies showed improvement and restored retinal physiology, and light adaptation (Abstract, Page 8623, Preparation of retinoids and oral gavage, Page 8364, Human studies, Results and Discussion, Bypassing the visual cycle, Page 8625, Page 8626, Human relevance.., Page 8627, Further Questions…). The improvement is inherent to the administration of the retinal regardless of the mechanism.

All the critical elements are taught by the cited reference and thus the claims are anticipated.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 16-19, 22, 36, 44, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Hooser et al. (Recovery of Visual Functions in a Mouse Model of Leber Congenital Amaurosis).

Van Hooser et al. teaches the use of 9-cis-retinal through oral, intravenous, and intraocular administration to a vertebrate for the treatment of lack of 11-cis-retinal. The studies showed improvement and restored light sensitivity with production and maintenance of rod photopigment for more than 6 months in the dark in the *Rpe65-/-* mice.

The most effective delivery system was gavage (oral), intravenous injection was also effective but could be rapidly eliminated by the kidneys, intraocular injection (local administration) was also an option (see full document). The improvement is inherent to the administration of the retinal regardless of the mechanism (see full document).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

17. Claims 16-19, 22, 44-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Chatzinoff et al. (U.S. Pat. No. 3196078).

Chatzinoff et al. teaches the use of 11-cis-isomer of vitamin A (retinal) or an ester for retinitis pigmentosa. Administration can be oral or parenteral (e.g. subcutaneous) forms. Several forms are exemplified and the 11-cis isomer has great value in combating retinitis pigmentosa (see full document, particularly claims). The improvement is inherent to the administration of the retinal regardless of the mechanism (see full document).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 20-21 and 35-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatzinoff et al. (U.S. Pat. No. 3196078) as applied to claims 16-19, 22, 44-46 above, in view of Kuksa et al. (Biochemical and Physiological properties of Rhodopsin Regenerated with 11-cis-6-Ring and 7-Ring-retinals), and further in view of Klimko (U.S. Pat. No. 6300328).

The teachings of Chatzinoff et al. are addressed above.

Chatzinoff et al. does not expressly teach the incorporation of a 11-cis-7-Ring neither retinal nor local administration of retinals.

Kuksa et al. teaches the biochemical and physiological effect of retinal analogs with different ring sizes that prevented isomerization around the C11 and C12 double bond. Kuksa taught that the 11-cis-7-ring did not isomerizes along the double bonds and appears to bind tightly with the opsin. Among the 11-cis-7 retinal isomers modeled is cycloheptatrienylidene 11-cis-locked retinal (see Figure 1, A, 3). Kuksa teaches that the constrained retinoids particularly the 11-cis-7 retinal has potential use to inactivate opsin in some retinal degeneration diseases. Specifically mentioned are conditions with mutations in the RPE65 gene such as Leber congenital amaurosis (LCA) and autosomal recessive retinitis pigmentosa (see full document).

Klimko teaches pharmaceutical forms for methods of administration that are known in the art for ophthalmic conditions (e.g. retinitis pigmentosa) including oral administration (e.g. tablets, capsules, solutions), parenteral use (e.g. solutions and suspensions), topical administration (e.g. solutions, suspensions, eye drops), and intraocular (includes retrobulbar or periocular injections or perfusion) or depot administration (Col. 6, lines 36, 45-55, 64-68, Col.7, lines 1, 23-26, 38-43).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize any 11-cis-7 retinal, particularly one exemplified or modeled for LCA or retinitis pigmentosa (both protein conformational disorders), as suggested by Kuksa, and produce the instant invention. It is obvious to utilize a 11-cis-7 retinal, particularly one modeled and known in the art, for retinitis pigmentosa or related disorders as Kuksa teaches that administration of these analogs have the potential to restore vision and maintaining useful vision.

One of ordinary skill in the art would have been motivated to do this because incorporation of compounds for improved and directed treatment of progressive blinding conditions is desirable.

It also would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize any one of the known methods and forms of administration known in the art, as suggested by Klimko, and produce the instant invention. It is obvious to utilize any method or mode of administration known in the art,

depending on the effectiveness of the compound, degree of toxicity, target area, optimal dosage levels, condition to be treated, and therapeutic profile desired.

One of ordinary skill in the art would have been motivated to do this because depending on the target area, dosage levels, condition to be treated, and therapeutic profile desired; different forms and methods of administration would be desired.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

20. Claims 16-22 and 35-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-11, 59, 62, 70-104 of copending Application No. 10/548612. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are broader than those of the copending application and would encompass the claims. The exceptions are the claims of the instant application reciting the specific retinal types that would anticipate the broad claims of the copending

application. It is noted that the methods recite only the administration of the compounds to the eye which are present in both set of claims

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. Claims 16-22 and 35-46 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612